PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/011122	05.10.2004	06.10.2003

International Patent Classification (IPC) or both national classification and IPC
G01N33/543, A61K31/427, C12Q1/68

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/011122

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2-15

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 2-15

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/011122

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1
Industrial applicability (IA)	Yes:	Claims	1
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III.

No written opinion will be formulated in respect of subject matter which is not covered by the search report

Re Item IV.

The separate inventions/groups of inventions are:

1. Claim 1
   Use of epothilone B in the manufacture of a medicament for the treatment of solid tumours.
2. Claims 2-15
   A method for predicting dierrhoea in a subject, kits for predicting diarrhoa according to said claims.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problems to be solved by the present application are to provide for (I) the treatment of solid tumors, more particularly in a selected patient population, wherein the patient population is selected on the basis of the gene expression profile of the patients, wherein the gene expression profile comprises the gene expression pattern of one or more genes that are predictive of the occurrence of diarrhoea in a patient following administration of epothilone B, i.e. a group of patients that does have a reduced proneness to drug-induced diarrhoea, (II) to provide for a method for predicting diarrhoea in a subject.

The proposed solution for the first problem is to use epothilone B, the proposed solution for the second problem is to provide for a method or kit comprising: (a) a reagent for detecting the gene expression pattern of one or more genes, wherein the one or more genes are selected from the group consisting of : (1) Interferon regulatory factor 5 (IRF5) ; (2) Cell division cycle 34 (CDC34); BCL2/adenovirus BIB 19kDa interacting protein 3-like (BNIP3L); Tubulin, beta (GenBank Accession Number V00599); 2,3-bisphosphoglycerate

mutase (BPGM); Aminolevulinate, delta-, synthase 2 (ALAS2); Selenium binding protein 1 (SELENBP1) ; and Solute carrier family 4, anion exchanger, member 1 (erythrocyte membrane protein band 3, Diego blood group) (SLC4A1) ; (3) Surfeit 2 (SURF2) ; Transmembrane 9 superfamily member 1 (TM9SF1) ; death-associated protein kinase 1 (DAPK1) ; RAP1A, a member of RAS oncogene family (RAP1A) ; down-regulator of transcription 1 (DR1) ; Janus kinase 1 (JAK1) ; tubulin, alpha (K-ALPHA-1) and zinc finger protein 36, C3H type, homolog (ZFP36); and (4) nuclear transcription factor Y, alpha (GenBank Accession Number AL031778) ; Transcription factor-like 4 (TCFL4) and mitogen-activated protein kinase kinase kinase kinase 2 NAP4K2).

(b) a container for the reagent; and (c) a written product on or in the container describing the use of the biomarker.

WO00/03024 discloses methods for diagnosing diarrhea. See the passages cited in the search report.

ROTHERMEL J; ET AL in SEMINARS IN ONCOLOGY, BETHESDA, MD, US, VOL. 30, NR 3, SUPPL 6, PG - 51-55, XP008039857 discloses that EPO906 (epothilone B) is a potent member of a new class of microtubule-stabilizing cytotoxic agents. EPO906 has shown anticancer activity both in vitro and in vivo against several cancer types. Diarrhea was the dose-limiting toxicity on both schedules. Tumor responses were seen in colorectal cancer as well as a variety of other tumor types, such as breast, ovarian, lung, etc. Consequently, the patient group that received treatment is the one with a reduced occurence of drug-induced diarrhoea. See the passages cited in the search report.

According to Article 3(4)(iii) PCT, an international application shall comply with "the prescribed requirement of unity of invention". This means, as explained in Rule 13.1 PCT, that the application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

From the above cited documents, it appears that the use of above specified compounds in relation to the treatment of above specified disorders, and methods for diagnosing diarrhea, irrespective of its etiology, is known in the prior art and can not fulfil the role of

special technical feature (general inventive concept) in the sense of Rule 13.2 PCT.

Accordingly there is no new technical effect linking the different groups of inventions.

In the present application no further technical feature can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions.

Consequently the present application lacks unity of invention.

As searching the other inventions would have caused a major additional searching effort, only the first invention was searched.

Re Item V.

1 Reference is made to the following documents:

D1 : ROTHERMEL JOHN ET AL: "EPO906 (epothilone B): a promising novel microtubule stabilizer." SEMINARS IN ONCOLOGY. JUN 2003, vol. 30, no. 3 Suppl 6, June 2003 (2003-06), pages 51-55, XP008039857 ISSN: 0093-7754

D2 : WITTMANN S ET AL: "Flavopiridol down-regulates antiapoptotic proteins and sensitizes human breast cancer cells to epothilone B-induced apoptosis" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 63, no. 1, 1 January 2003 (2003-01-01), pages 93-99, XP002290844 ISSN: 0008-5472

D3 : WO 00/03024 A (THE ROCKEFELLER UNIVERSITY; THE ADVANCED RESEARCH AND TECHNOLOGY INSTI) 20 January 2000 (2000-01-20)

D4 : WARTMANN M ET AL: "THE BIOLOGY AND MEDICINAL CHEMISTRY OF EPOTHILONES" CURRENT MEDICINAL CHEMISTRY. ANTI-CANCER AGENTS, BENTHAM SCIENCE PUBLISHERS, HILVERSUM, NL, vol. 2, no. 1, January 2002 (2002-01), pages 123-148, XP009017278 ISSN: 1568-0118

D5 : ALTMANN KARL-HEINZ: "Epothilone B and its analogs - a new family of anticancer agents." MINI REVIEWS IN MEDICINAL CHEMISTRY. MAR 2003,

vol. 3, no. 2, March 2003 (2003-03), pages 149-158, XP008050865 ISSN: 1389-5575

2 INDEPENDENT CLAIM 1

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.
Document D1 discloses (see the passages cited in the search report) that EPO906 (epothilone B) is a potent member of a new class of microtubule-stabilizing cytotoxic agents. EPO906 has shown anticancer activity both in vitro and in vivo against several cancer types. Diarrhea was the dose-limiting toxicity on both schedules. Tumor responses were seen in colorectal cancer as well as a variety of other tumor types, such as breast, ovarian, lung, etc. Consequently, the patient group that received treatment is the one with a reduced occurence of drug-induced diarrhoea.

2.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.
Document D2 discloses (see the passages cited in the search report) that Flavopiridol down-regulates antiapoptotic proteins and sensitizes human breast cancer cells to epothilone B-induced apoptosis.

2.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.
Document D4 discloses (see the passages cited in the search report) that epothilones, unlike paclitaxel (Taxol), are equally active against drug-sensitive and multidrug-resistant cell lines in vitro and epothilone B has also shown potent in vivo antitumor activity in Taxol-resistant human tumor models.

2.4 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.
Document D5 discloses (see the passages cited in the search report) that a number of compounds, including natural epothilone B, deoxyepothilone B, and epothilone B lactam (BMS-247550) have also been reported to exhibit profound in vivo antitumor

activity in animal models. Two of these compounds, natural epothilone B and epothilone B lactam (BMS-247550) have advanced to clinical studies in humans.

3. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 does not involve an inventive step in the sense of Article 33(3) PCT.

3.1 The fact that diarrhoea is the dose-limiting side-effect in the cancer treatment with epothilone B is well documented from D1. Consequently the skilled practician would select patients to be treated on the basis of the occurence of diarrhoea in said patients.